

What is already known on this topic

Third generation oral contraceptives have been reported to increase the risk of venous thrombosis compared with second generation oral contraceptives

The findings have been vigorously debated, with suggestions that the results can be explained by confounding or bias, or both.

What this study adds

Women taking third generation oral contraceptives have a 1.7-fold increased risk of venous thrombosis compared with those taking second generation oral contraceptives

Risk is highest in first time users

The biases were not large enough to account for the observed results

Conclusion

Our meta-analysis supports the view that third generation oral contraceptives are associated with a 1.7-fold increased risk of venous thrombosis compared with second generation oral contraceptives. The risk is highest in first time users. Although confounding can never be excluded with certainty in observational studies, it seems that the biases that have been suggested and examined are not sufficient to account for the results.

Contributors: JMK participated in the design, execution, and analysis of the study and writing the paper. AA and DEG initiated the study, participated in designing, analysing, and reporting the study, and supervised all aspects of the study. DEG is the guarantor

Funding: None.

Competing interests: JMK has worked on a study into second and third generation contraceptives sponsored by the Netherlands Thrombosis Foundation.

- 1 World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Venous thromboembolic disease and combined oral contraceptives: results of international multicentre case-control study. *Lancet* 1995;346:1575-82.
- 2 Jick H, Jick SS, Gurewich V, Myers MW, Vasilakis C. Risk of idiopathic cardiovascular death and nonfatal venous thromboembolism in women using oral contraceptives with differing progestagen components. *Lancet* 1995;346:1589-93.
- 3 Bloemenkamp KW, Rosendaal FR, Helmerhorst FM, Buller HR, Vandenbroucke JP. Enhancement by factor V Leiden mutation of risk of deep-vein thrombosis associated with oral contraceptives containing a third-generation progestagen. *Lancet* 1995;346:1593-6.
- 4 Spitzer WO, Lewis MA, Heinemann LA, Thorogood M, MacRae KD. Third generation oral contraceptives and risk of venous thromboembolic disorders: an international case-control study. *BMJ* 1996;312:83-8.

- 5 Farmer RD, Lawrenson RA, Thompson CR, Kennedy JG, Hambleton IR. Population-based study of risk of venous thromboembolism associated with various oral contraceptives. *Lancet* 1997;349:83-8.
- 6 Suissa S, Blais L, Spitzer WO, Cusson J, Lewis M, Heinemann L. First-time use of newer oral contraceptives and the risk of venous thromboembolism. *Contraception* 1997;56:141-6.
- 7 Lidegaard O, Edstrom B, Kreiner S. Oral contraceptives and venous thromboembolism. A case-control study. *Contraception* 1998;57:291-301.
- 8 Spitzer WO. The aftermath of a pill scare: regression to reassurance. *Hum Reprod Update* 1999;5:736-45.
- 9 Farley TM, Meirik O, Collins J. Cardiovascular disease and combined oral contraceptives: reviewing the evidence and balancing the risks. *Hum Reprod Update* 1999;5:721-35.
- 10 Petitti DB. Statistical methods in meta-analysis. In: *Meta-analysis, decision analysis, and cost-effectiveness analysis*. New York: Oxford University Press, 1994:106-110.
- 11 Bloemenkamp KW, Rosendaal FR, Buller HR, Helmerhorst FM, Colly LP, Vandenbroucke JP. Risk of venous thrombosis with use of current low-dose oral contraceptives is not explained by diagnostic suspicion and referral bias. *Arch Intern Med* 1999;159:65-70.
- 12 World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Effect of different progestagens in low oestrogen oral contraceptives on venous thromboembolic disease. *Lancet* 1995;346:1582-8.
- 13 Farmer RD, Todd JC, Lewis MA, MacRae KD, Williams TJ. The risks of venous thromboembolic disease among German women using oral contraceptives: a database study. *Contraception* 1998;57:67-70.
- 14 Herings RM, Urquhart J, Leufkens HG. Venous thromboembolism among new users of different oral contraceptives. *Lancet* 1999;354:127-128.
- 15 Lewis MA, MacRae KD, Kuhl-Habich D, Bruppacher R, Heinemann LA, Spitzer WO. The differential risk of oral contraceptives: the impact of full exposure history. *Hum Reprod* 1999;14:1493-9.
- 16 Farley TM, Meirik O, Poulter NR, Chang CL, Marmot MG. Oral contraceptives and thrombotic diseases: impact of new epidemiological studies. *Contraception* 1996;54:193-8.
- 17 Todd J, Lawrenson R, Farmer RD, Williams TJ, Leydon GM. Venous thromboembolic disease and combined oral contraceptives: a reanalysis of the MediPlus database. *Hum Reprod* 1999;14:1500-5.
- 18 Farmer RD, Lawrenson RA, Todd JC, Williams TJ, MacRae KD, Tyrer F, et al. A comparison of the risks of venous thromboembolic disease in association with different combined oral contraceptives. *Br J Clin Pharmacol* 2000;49:580-90.
- 19 Jick H, Kaye JA, Vasilakis-Scaramozza C, Jick SS. Risk of venous thromboembolism among users of third generation oral contraceptives compared with users of oral contraceptives with levonorgestrel before and after 1995: cohort and case-control analysis. *BMJ* 2000;321:1190-5.
- 20 Vasilakis C, Jick SS, Jick H. The risk of venous thromboembolism in users of postcoital contraceptive pills. *Contraception* 1999;59:79-83.
- 21 Juni P, Witschi A, Bloch R, Egger M. The hazards of scoring the quality of clinical trials for meta-analysis. *JAMA* 1999;282:1054-60.
- 22 Vandenbroucke JP. Scoring the quality of clinical trials. *JAMA* 2000;283:1422-3.
- 23 Weber W. Study on risks of third generation pill "kept secret by industry." *Lancet* 2001;357:779.
- 24 Vandenbroucke JP, Helmerhorst FM, Bloemenkamp KW, Rosendaal FR. Third-generation oral contraceptive and deep venous thrombosis: from epidemiologic controversy to new insight in coagulation. *Am J Obstet Gynecol* 1997;177:887-91.
- 25 Walker AM. Newer oral contraceptives and the risk of venous thromboembolism. *Contraception* 1998;57:169-81.
- 26 Stelfox HT, Chua G, O'Rourke K, Detsky AS. Conflict of interest in the debate over calcium-channel antagonists. *N Engl J Med* 1998;338:101-6.
- 27 Rochon PA, Gurwitz JH, Simms RW, Fortin PR, Felson DT, Minaker KL, et al. A study of manufacturer-supported trials of nonsteroidal anti-inflammatory drugs in the treatment of arthritis. *Arch Intern Med* 1994;154:157-63.
- 28 Farmer RD, Lawrenson RA, Todd JC, Williams TJ, MacRae K. Oral contraceptives and venous thromboembolic disease. Analyses of the UK General Practice Research Database and the UK Mediplus database. *Hum Reprod Update* 1999;5:688-706.

(Accepted 7 June 2001)

One hundred years ago The doctor in politics

The medical profession is treated by politicians as a negligible quantity, but this is partly because it does not know, and partly because it does not care to use, its power. What doctors could do if they chose to use the legitimate influence which they have, is shown by an incident in a recent electoral campaign in America. The defeat of Governor Charles S. Thomas, of Colorado, for a seat in the United States Senate was, according to the *Maryland Medical Journal*, due to the influence of the medical profession,

who determined to punish him for an insulting veto message. The doctors all over the State worked for democratic and fusion candidates who would pledge themselves to oppose Governor Thomas. The Governor was perfectly sure of his nomination until the Legislature assembled, when he found that he lacked four votes. The bitterness of his defeat was doubtless increased by the fact that it was due to the action of the despised doctors.

(*BMJ* 1901;i:1038)